REMARKS

Claims 1-3 and 6-8 are pending in the application. Claims 4-5 and 9-32 have been withdrawn without prejudice to Applicants' right to prosecute them in one or more divisional applications. Claim 1 has been amended and is now directed to a method for preventing or treating epithelial tissue damage comprising identifying a patient in need of epithelial tissue protection or treatment, obtaining a substance that prevents or treats epithelial tissue damage, comprising: a polynucleotide antisense to a sequence comprising the glucosylceramide synthase gene and/or the glucosylceramide synthase mRNA, and administering the substance to said patient. Support for the amendment can be found in the specification at page 7, lines 3-14; page 9, lines 13 - page 10, line 24; page 11, line 27 – page 12, line 6 and page 12, lines 12-19, for example. Claim 6 has been amended and is now directed to a method for making a pharmaceutical composition for preventing or treating epithelial tissue damage. In addition, to the passages just recited, support for the amendment can be found at page 12, line 25 – page 13, line 21, for example. It is believed that no new matter has been added by way of amendment.

The specification has been amended to include sequence identifiers for the recited nucleotide sequences. The figure on page 36 has been denoted as such and a new description has been included in the Brief Description of Figures. Table numbers have been assigned to the tables on pages 30, 35 and 37-38.

Claims 1 and 6 have been amended to place them in conformity with the restriction requirement.

Claims 1-3 and 6-8 stand rejected under 35 U.S.C. § 112, first paragraph, for failing to meet the written description requirement. Applicants request that this rejection be reconsidered and withdrawn for the following reasons. Of the rejected claims only Claims 1 and 6 are independent. Claim 1 is now directed to a method for preventing or treating epithelial tissue damage comprising identifying a patient in need of epithelial tissue protection or treatment, obtaining a substance that prevents or treats epithelial tissue damage, comprising: a polynucleotide antisense to a sequence comprising the glucosylceramide synthase gene and/or the glucosylceramide synthase mRNA, and administering the polynucleotide to said patient. Claim 6 is directed to the manufacture of a pharmaceutical composition for preventing or treating epithelial tissue damage that contains the same substance.

The Office action took the position that the application must contain a number of polynucleotide subtstances to provide evidence of possession of the invention. Applicants submit that oligonucleotide design for RNAi knockouts and for antisense technology is now well established. This is evidenced by the fact the numerous websites on the internet that are available to help select suitable oligonucleotides. It is well known in the art that many many oligonucleotides are available for both RNAi and antisense strategies. A sampling of web-based oligonucleotide design sites is provided below:

- http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&list_uids=15215365&cmd=Retrieve&indexed=google
    - Nucleic Acids Res. 2004 Jul 1;32(Web Server issue):W130-4.
- http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?itool=abstractplus&db=pubmed&cmd=Retrieve&dopt=abstractplus&list_uids=16722778
    - Appl Bioinformatics. 2006;5(2):121-
- http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?itool=abstractplus&db=pubmed&cmd=Retrieve&dopt=abstractplus&list_uids=15215366
    - Nucleic Acids Res. 2004 Jul 1;32(Web Server issue):W135-41.

In fact, oligonucleotide manufacturers include such programs on their websites and guarantee that oligonucleotide sets ordered from their sites will function. See for example the website for oligonucleotide design at Integrated DNA Technologies, Inc.:

- http://www.idtdna.com/SciTools/SciTools.aspx

This website includes design programs for RNAi and antisense oligonucleotides, which is an even a more established technology.

As can be seen from a review of these sites, all that is required for the design of such oligonucleotides is knowledge of the sequence of a gene or RNA transcript. Using websites such as this 6a researcher can simply load the gene or mRNA sequence information onto the site in order to obtainn a number of oligonucleotides that will work for either antisense or RNAi knockout strategies. This entire process occurs within minutes on the website and if that researcher then orders several of those oligonucleotides they will have the oligonucleotides the next morning. This process requires little in the way of skill or experimentation. The art is well

enough advanced that it is a virtual certainty that one of skill will find a number of oligonucleotides that will work to reduce expression of a target gene.

It is well established that the written description requirement does not require disclosure of methods or techniques that are well known in the art and it goes without saying that the design and manufacture of RNAi or antisense oligonucleotides which can be carried out on publicly available websites within a day by people having less than ordinary skill in the art is certainly well known in the art. Applicants submit that the present application has disclosed all that is necessary to satisfy the written description requirement and respectfully request that the rejection be withdrawn.

Claims 2-3 stand rejected under 35 U.S.C. § 112, second paragraph, as indefinite. With respect to Claim 2, the phrase "reducing at least one of the transcription and translation of the CD_{1d} gene" was considered indefinite because they reflect processes rather than products. Although, Applicants submit that one could refer to one or the other of the respective processes, Claim 2 has been amended to refer to a reduction in transcription. With respect to Claim 3, the list of the sources of compounds was considered inappropriate. While it is submitted the RNAi oligonucleotides were first discovered in plants and in plant material and has since been shown to occur in many other organisms and contexts, Claim 3 has been amended to specifically refer to RNAi oligonucleotides.

The Office action objected to Claim 6 on the basis that it was a duplicate of Claim 1. Claim 6 now refers to a method of preparing a pharmaceutical composition and is distinct from a method of treatment as in Claim 1.

Claims 1, 3, and 6 stand rejected under 35 U.S.C. § 102(a) as anticipated by *Di Sano* as evidenced by *Nieda* and *Balreira*. The Office action took the position that *Di Sano* disclosed a glucosylceramide synthase antisense vector that downregulates glucosylceramide synthase activity. Applicants respectfully request that the rejection be withdrawn for the following reasons. *Di Sano* fails to disclose or suggest the use of its composition for preventing or treating epithelial tissue damage in a patient needing such a treatment. Thus, independent Claims 1 and 6 are distinct from *Di Sano* and are not made obvious by *Di Sano*. Claim 3, which depends from Claim 1, is patentable for at least the same reasons.

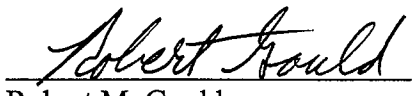
Claims 1, 3, and 6 stand rejected under 35 U.S.C. § 102(a) as anticipated by *Deng* as evidenced by *Nieda* and *Balreira*. The Office action took the position that *Deng* disclosed a glucosylceramide synthase antisense vector that downregulates glucosylceramide synthase activity when transfected into mammalian cells. Applicants respectfully request that the rejection be withdrawn for the following reasons. *Deng* fails to disclose or suggest the use of its composition for preventing or treating epithelial tissue damage in a patient needing such a treatment. Thus, independent Claims 1 and 6 are distinct from *Deng* and are not made obvious by *Deng*. Claim 3, which depends from Claim 1, is patentable for at least the same reasons.

Claims 1, 3, and 6 stand rejected under 35 U.S.C. §102(a) as anticipated by *Liu*. The Office action took the position that *Liu* disclosed a glucosylceramide synthase antisense vector that downregulates glucosylceramide synthase activity when transfected into mammalian cells. Applicants respectfully request that the rejection be withdrawn for the following reasons. *Liu* fails to disclose or suggest the use of its composition for preventing or treating epithelial tissue damage in a patient needing such a treatment. Thus, independent Claims 1 and 6 are distinct from *Liu* and are not made obvious by *Liu*. Claim 3, which depends from Claim 1, is patentable for at least the same reasons.

Applicants submit that they have made an earnest effort to place the application in allowable form and request that the application be passed to issue. The Commissioner is hereby authorized to charge deposit account 02-1818 for any fees which are due and owing.

Respectfully submitted,

BELL, BOYD & LLOYD LLP

BY 

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Dated: April 4, 2007